Edwards Advisory Committee Slides Shown

FDA-CSDP

June 13, 2012

Antithrombotic Medications at Discharge: Non-stroke Patients (AT Population)

Medication Regimen	TAVR N = 321		AVR N = 296	
	With Medication	Without Medication	With Medication	Without Medication
Aspirin alone	14.0%	86.0%	22.3%	77.7%
Antiplatelet alone	9.3%	90.7%	2.4%	97.6%
Anticoagulants alone	2.2%	97.8%	5.7%	94.3%
DAP Therapy	21.2%	78.8%	7.4%	92.6%
Anticoagulants with aspirin or antiplatelets	13.1%	86.9%	12.8%	87.2%
Any antithrombotic regimen	59.8%	40.2%	50.7%	49.3%

Discharge Medication: Antiplatelets and Antithrombotics

Discharge Medication	TAVR N = 341	AVR N = 317
ASA	13.5%	21.4%
ASA/Coumadin	10.6%	11.7%
ASA/Plavix	25.8%	9.5%
Coumadin	1.5%	5.0%
Plavix	9.1%	2.2%
None (or other)	39.6%	50.2%

CEC-Definition of Major Bleeding

Major bleeding event was the occurrence of at least one of the following events:

- Caused death
- Caused hospitalization or prolonged hospitalization ≥ 24 hours due to treatment for bleeding
- Required pericardiocentesis or open and/or endovascular procedure for repair or hemostasis
- Caused permanent disability (e.g., blindness, paralysis, hearing loss)
- Required transfusion of > 3 units of blood within 24 hour period.

Baseline Characteristics: PV Leak None/Trace Cohorts – TAVR vs AVR (1 of 2)

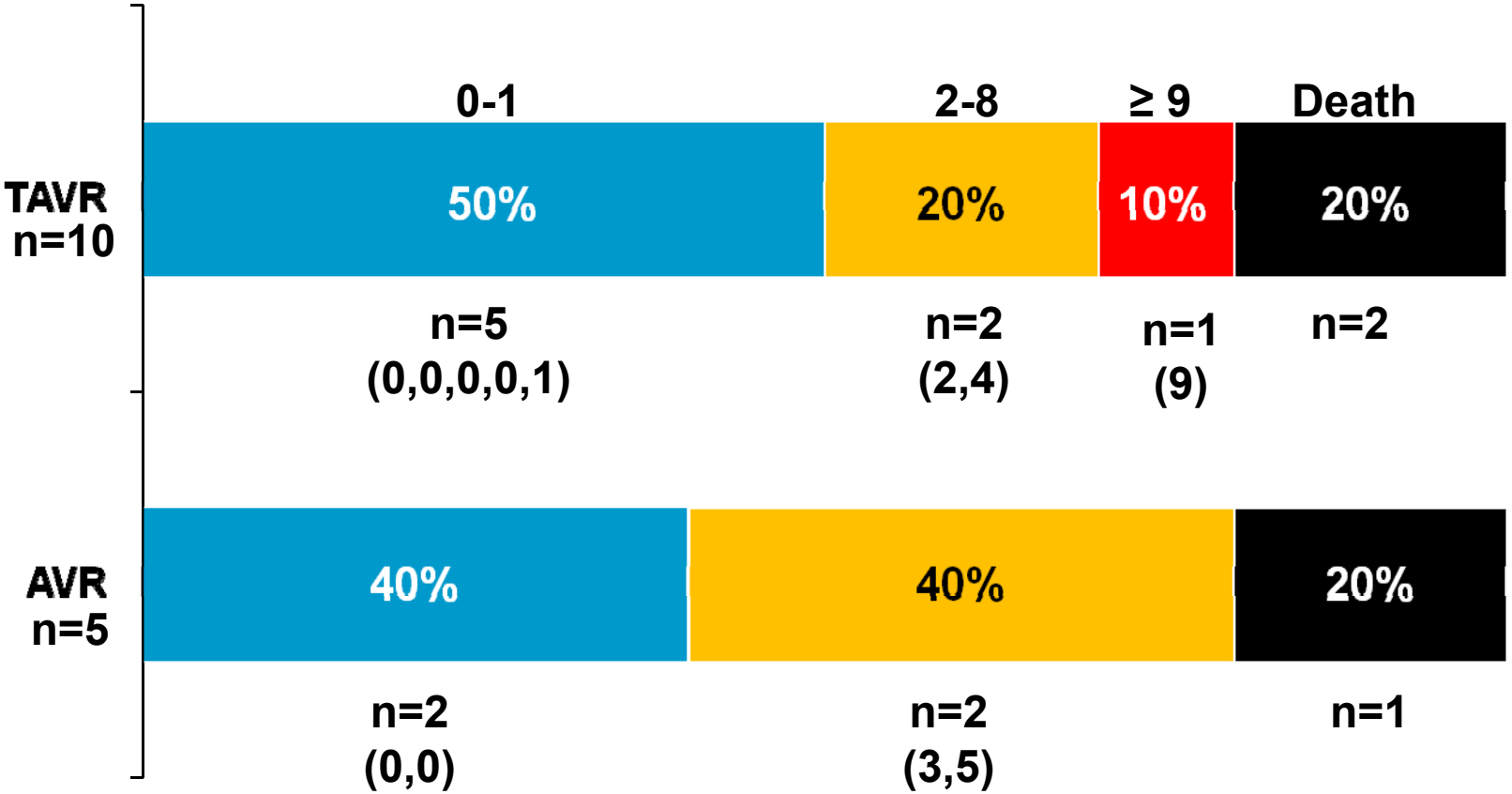
Characteristic	TAVR (N=158)	AVR (N=271)	p-value
Age - years	83.4 ± 6.7	84.5 ± 6.4	0.09
Male sex - no./total no. (%)	82/158 (51.9%)	152/271 (56.1%)	0.42
STS score	11.6 ± 3.0	11.7 ± 3.4	0.74
Logistic EuroSCORE	28.9 ± 16.4	29.4 ± 15.4	0.75
NYHA class - no./total no. (%)	158/158 (100.0%)	271/271 (100.0%)	
II	10/158 (6.3%)	14/271 (5.2%)	0.67
III	65/158 (41.1%)	126/271 (46.5%)	0.31
IV	83/158 (52.5%)	131/271 (48.3%)	0.42
Coronary artery disease - no./total no. (%)	110/158 (69.6%)	207/271 (76.4%)	0.14
Previous MI - no./total no. (%)	41/158 (25.9%)	78/269 (29.0%)	0.58
Prior CABG - no./total no. (%)	71/158 (44.9%)	124/271 (45.8%)	0.92
Prior PCI - no./total no. (%)	51/157 (32.5%)	84/270 (31.1%)	0.83
Prior BAV - no./total no. (%)	14/158 (8.9%)	27/271 (10.0%)	0.87
Peripheral vascular disease - no./total no. (%)	66/157 (42.0%)	112/265 (42.3%)	>0.999
Cerebral vascular disease - no./total no. (%)	40/144 (27.8%)	73/252 (29.0%)	0.82

Brain Imaging: Early Strokes

Characteristic	TAVR (n=15)	AVR (n=8)
MRI	**4**	**3**
CT*	**10****	**5**
Hemorrhagic Transformation	**3** (2 Petechial, 1 Focal)	**0**
Parenchymal Hemorrhage	**0**	**0**

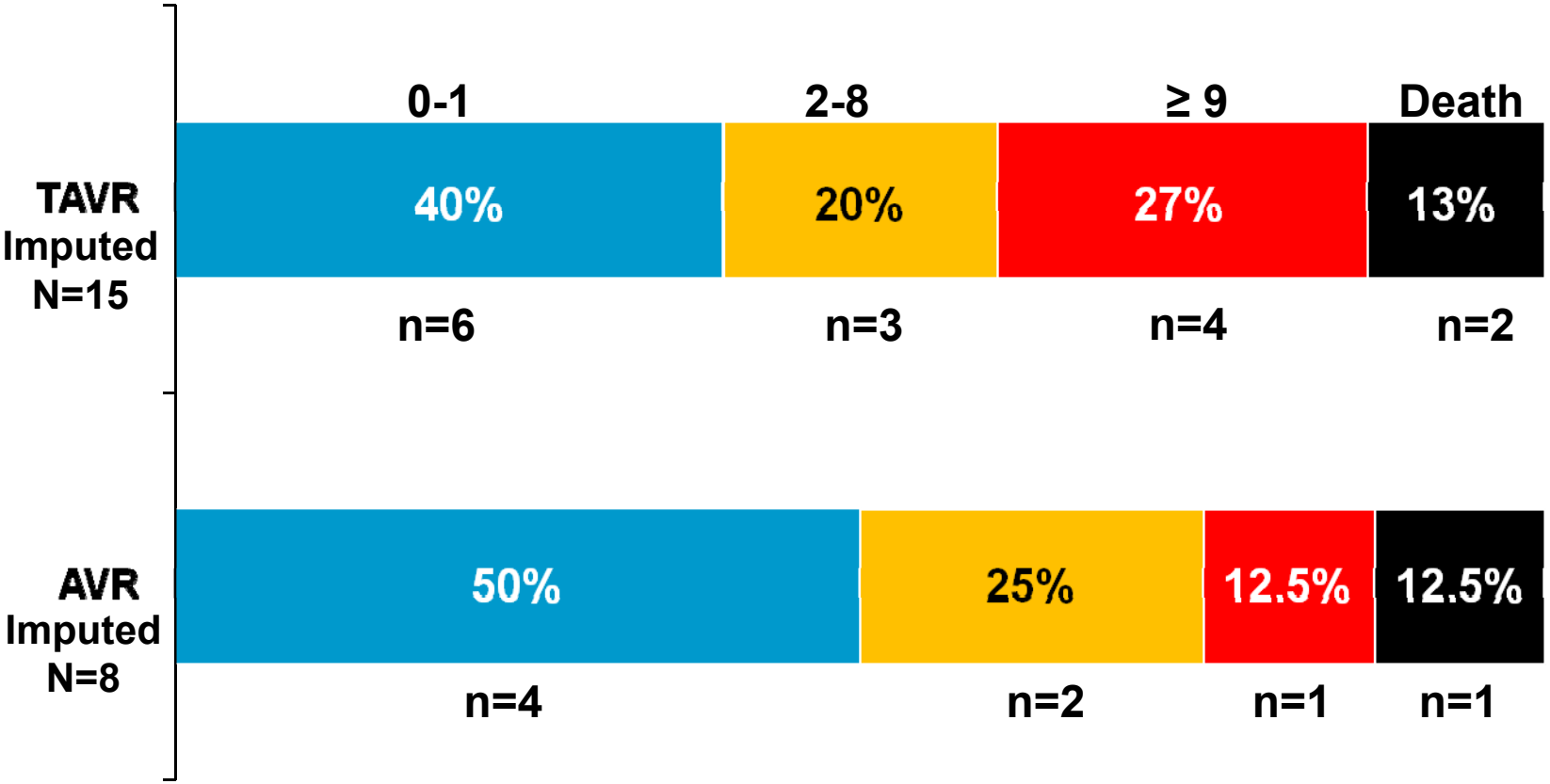
* Patient 2106 had no brain imaging due to unresponsiveness.
** One CT was done too early and the patient died in the setting of a large focal deficit.

NIH Stroke Scale at 30 days
TAVR vs AVR



AT Population

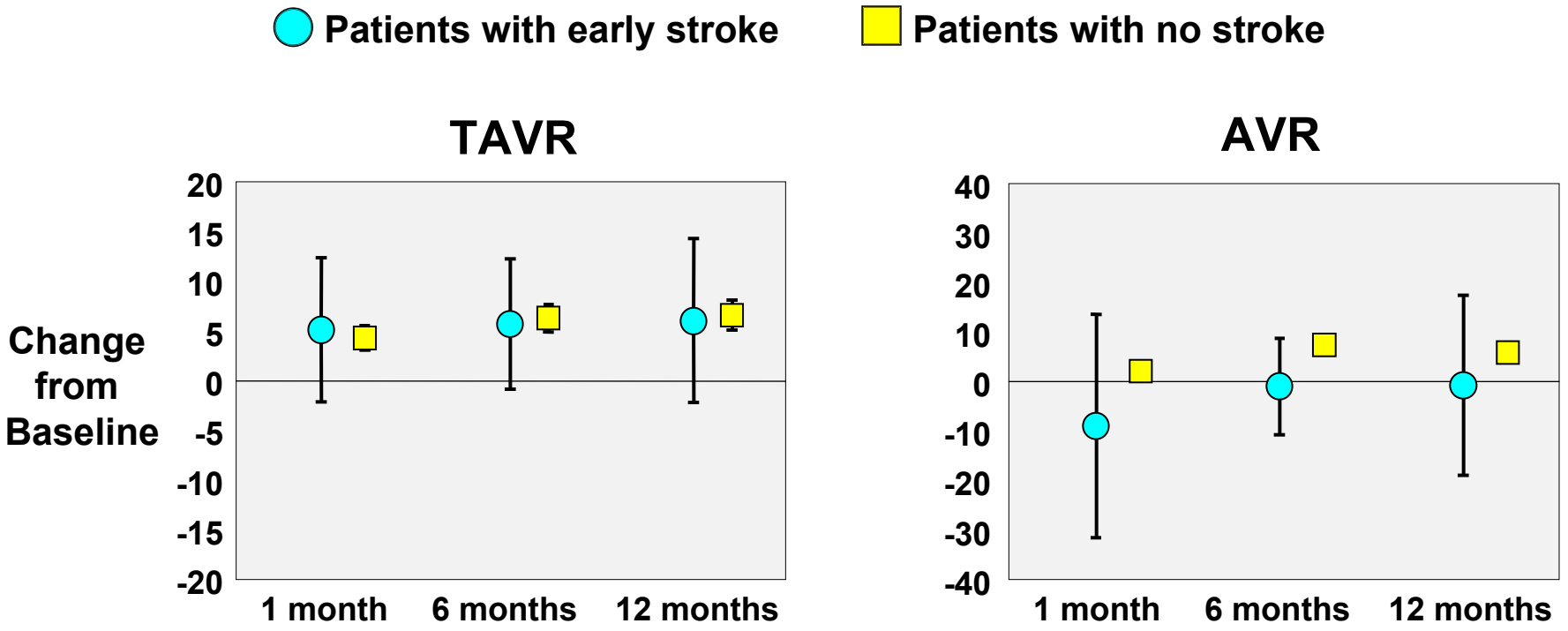
NIH Stroke Scale at 30 days
TAVR vs AVR Imputed Missing Data



AT Population

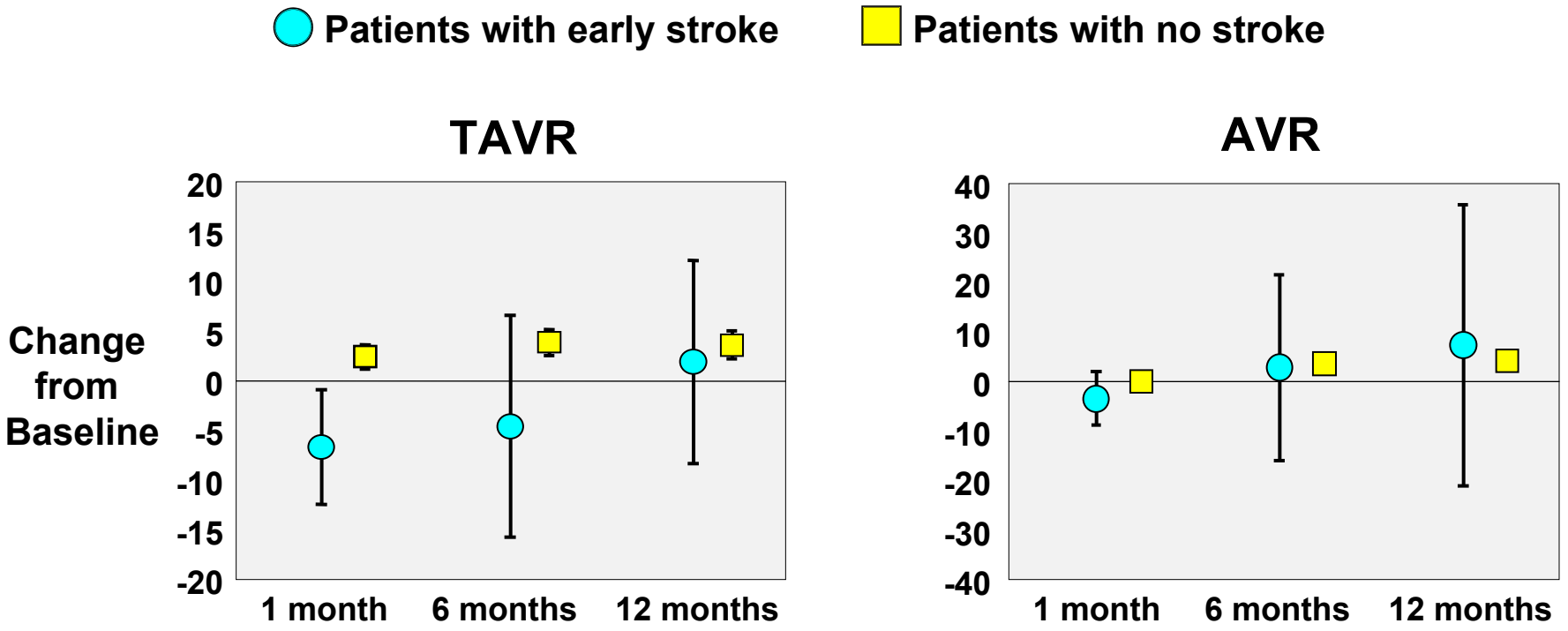
Stroke Outcomes: Quality of Life

SF-12 Physical QoL Score



Stroke Outcomes: Quality of Life

SF-12 Mental QoL Score



Transcranial Doppler Sound Detection of Cerebral Microembolism during Transapical Aortic Valve Implantation (Figures)

Table 3 Transcranial Doppler: high-intensity transient signals [HITS] [mean ± SD (range min-max)].

	Right side: middle cerebral artery	Left side: middle cerebral artery
Period of recording (min)	122 ± 47 (49–258)	
Total number of HITS	435 ± 922 (9–5765)	471 ± 996 (24–6432)
Total number of HITS (both sides)	730 ± 1717 (33–12197)	
Transfemoral pigtail catheter placement	6 ± 19 (0–167)	5 ± 7 (0–36)
14-Fr soft sheath insertion	3 ± 9 (0–55)	4 ± 11 (0–68)
Placement of a transaortic stiff guide (Amplatz Super Stiff, 035″, 260 cm)	9 ± 14 (0–66)	6 ± 12 (0–42)
Balloon valvuloplasty	21 ± 23 (0–99)	11 ± 18 (0–89)
Balloon valvuloplasty (total)	34 ± 33.8 (0–188)	
26-Fr transapical valve delivery system	8 ± 11 (0–51)	5 ± 12 (0–56)
Prosthetic valve deployment	26 ± 28 (0–114)	13 ± 25 (0–121)
Prosthetic valve deployment (total)	46 ± 44 (0–235)	
Removal of the transapical delivery system	5 ± 14 (0–52)	6 ± 10 (0–59)

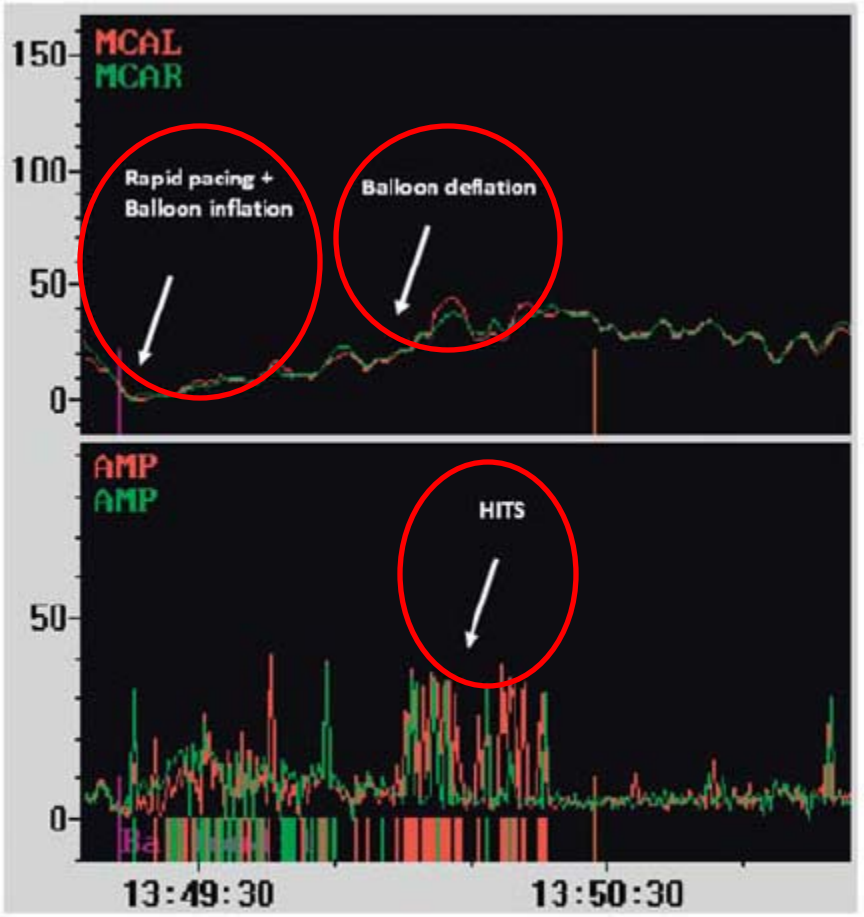


Fig. 1 Typical screen findings of transcranial Doppler examinations during balloon valvuloplasty. The upper screen shows flow velocity in the left (MCAL) and right (MCAR) middle cerebral artery. The lower screen (AMP) shows flow accelerations corresponding to potential embolic signals.

Comparison of current and new delivery catheters indicating marked differences in tip

RetroFlex 1

RF1

- Blunt tip can result in difficult tracking and traversing diseased arch
- Required more aggressive redilatation to ensure crossability
- Majority of PARTNER Randomized data utilized RF1

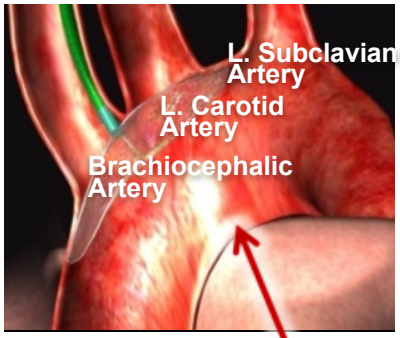
RetroFlex 3

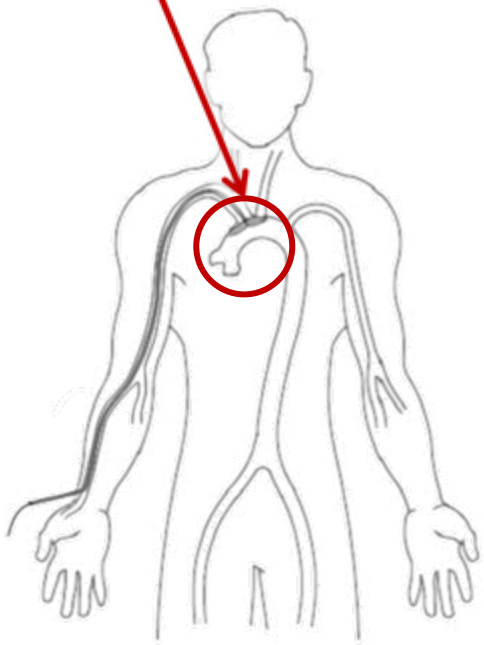
RF3

- Tapered nosecone improved ease of crossing of native valve and diseased arch
- Less aggressive dilatation required as result
- SAPIEN Control catheter In PARTNER IIB

Embrella Device Features

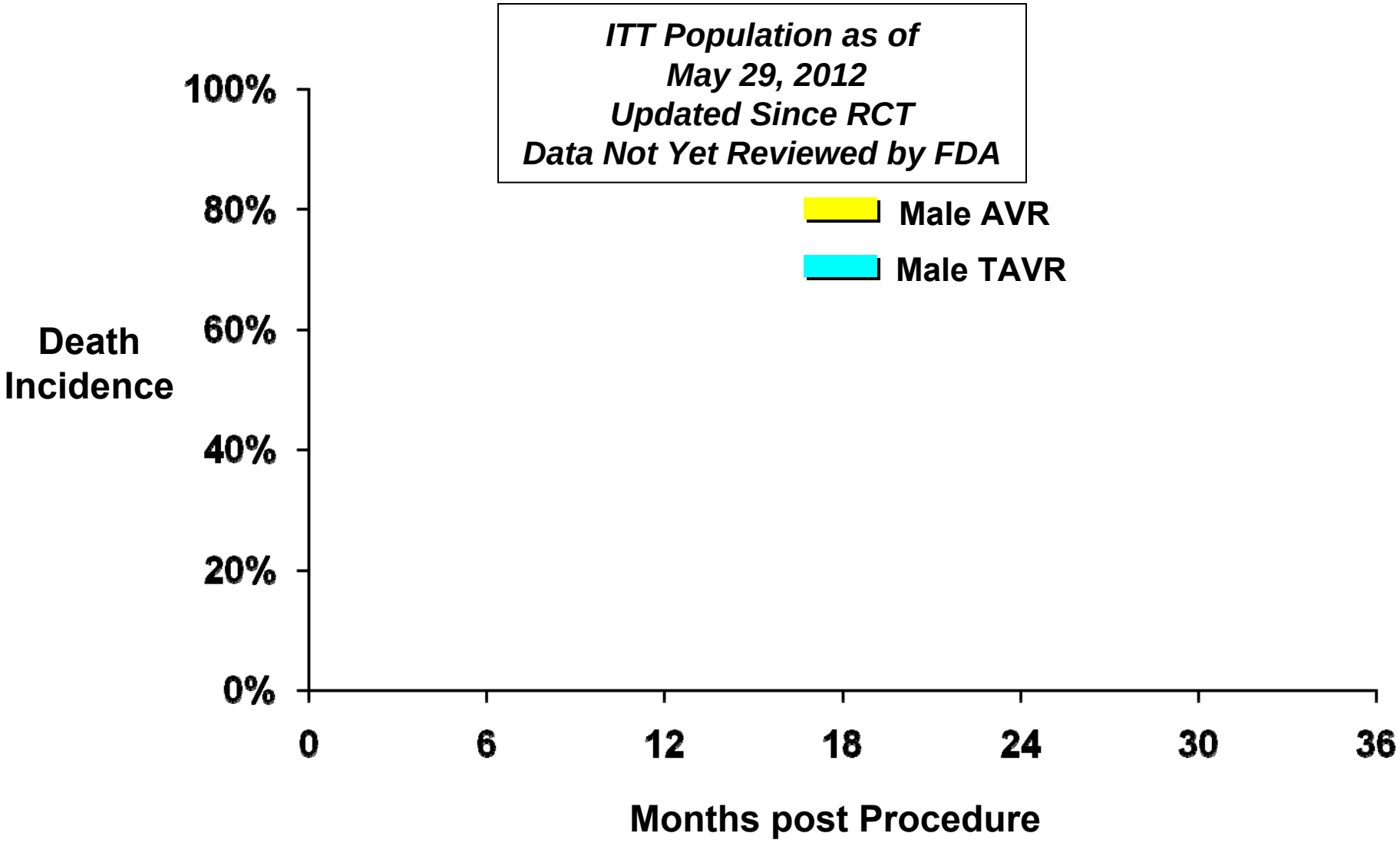
- **Design features ensure emboli deflection without interfering with TAVI procedure**
  - 6F sheath delivered via the right radial or brachial artery
  - Permits blood flow to the cerebral arteries while deflecting emboli
  - One size: designed to cover brachiocephalic and left carotid arteries



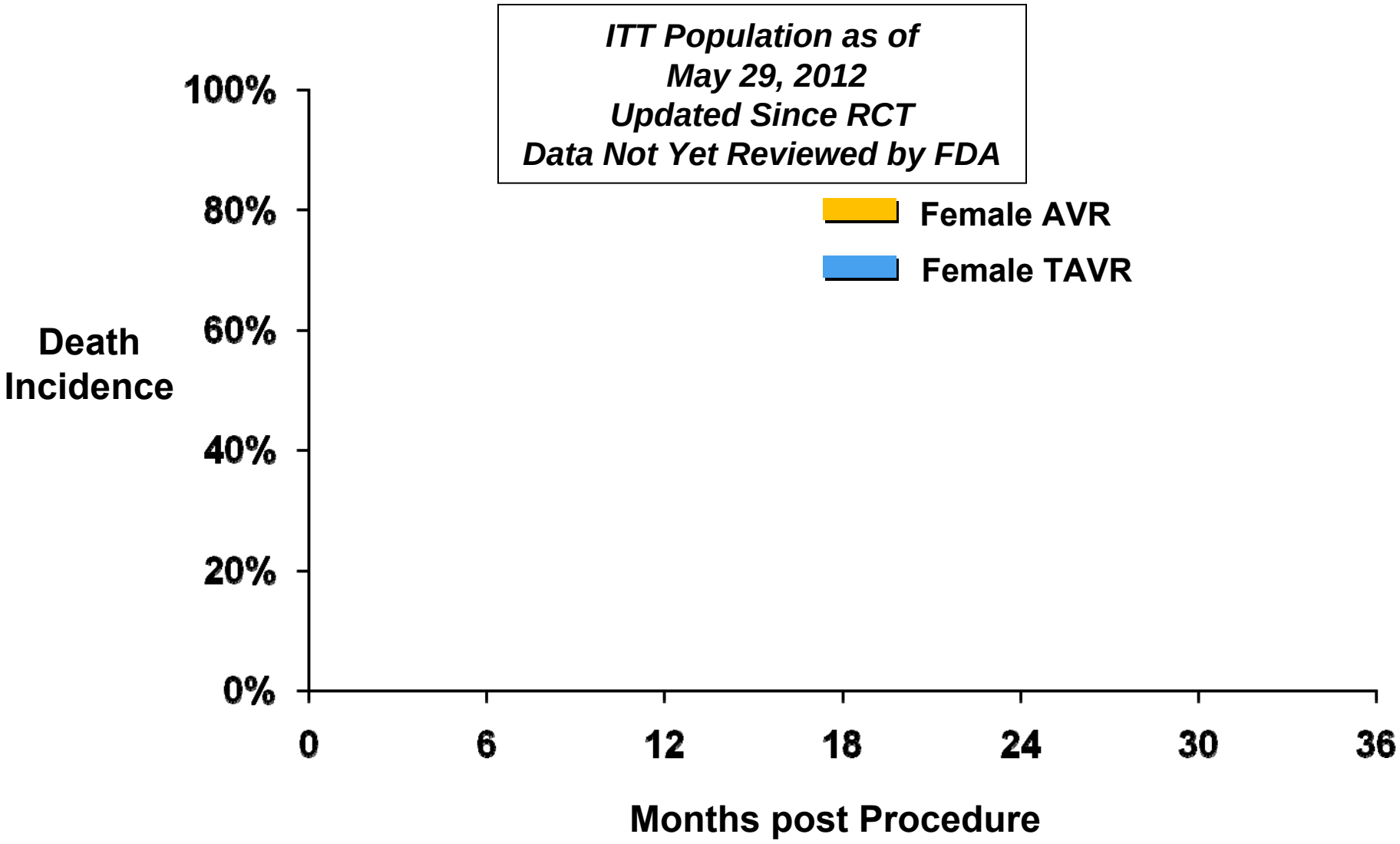


Features	
Access	Radial
Position	Aorta
Coverage Area	Brachiocephalic & LCC
Mechanism	Deflection
Type of Device	Porous, polyurethane membrane
Size	6F
Pore Size	100 microns

Death by Gender: Male

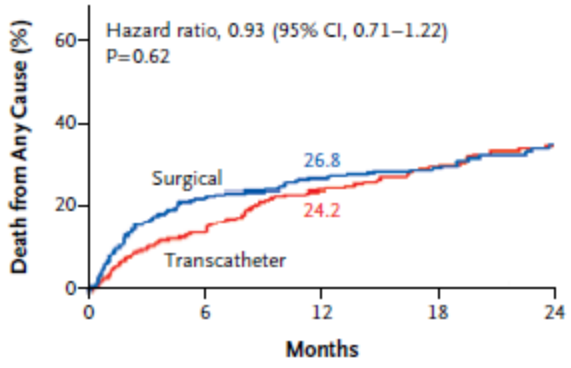


Death by Gender: Female



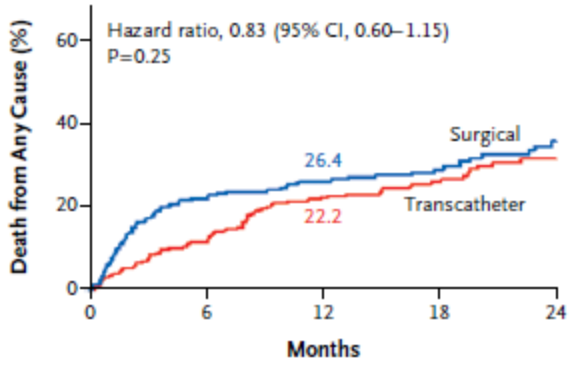
Time-to-Event Curves for Primary End Point and Other Selected End Points

A Death from Any Cause, All Patients



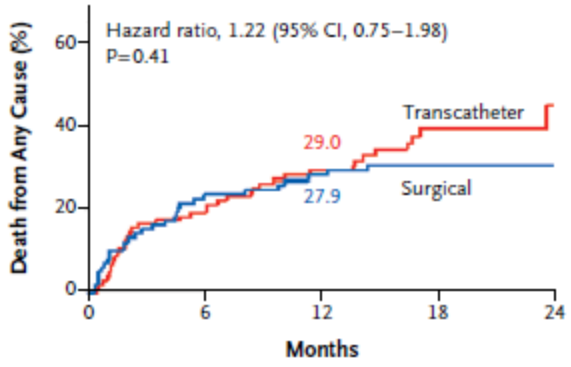
No. at Risk					
Transcatheter	348	298	260	147	67
Surgical	351	252	236	139	65

B Death from Any Cause, Transfemoral-Placement Cohort



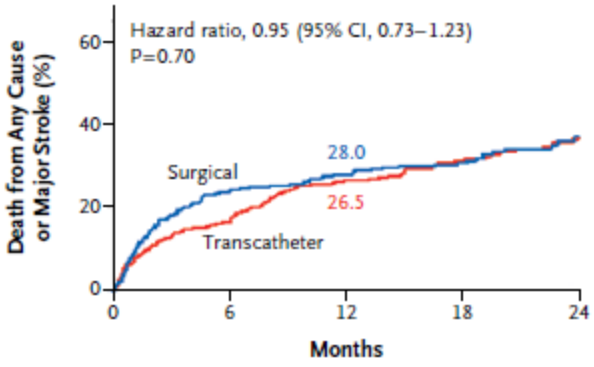
No. at Risk					
Transcatheter	244	215	188	119	59
Surgical	248	180	168	109	56

C Death from Any Cause, Transapical-Placement Cohort



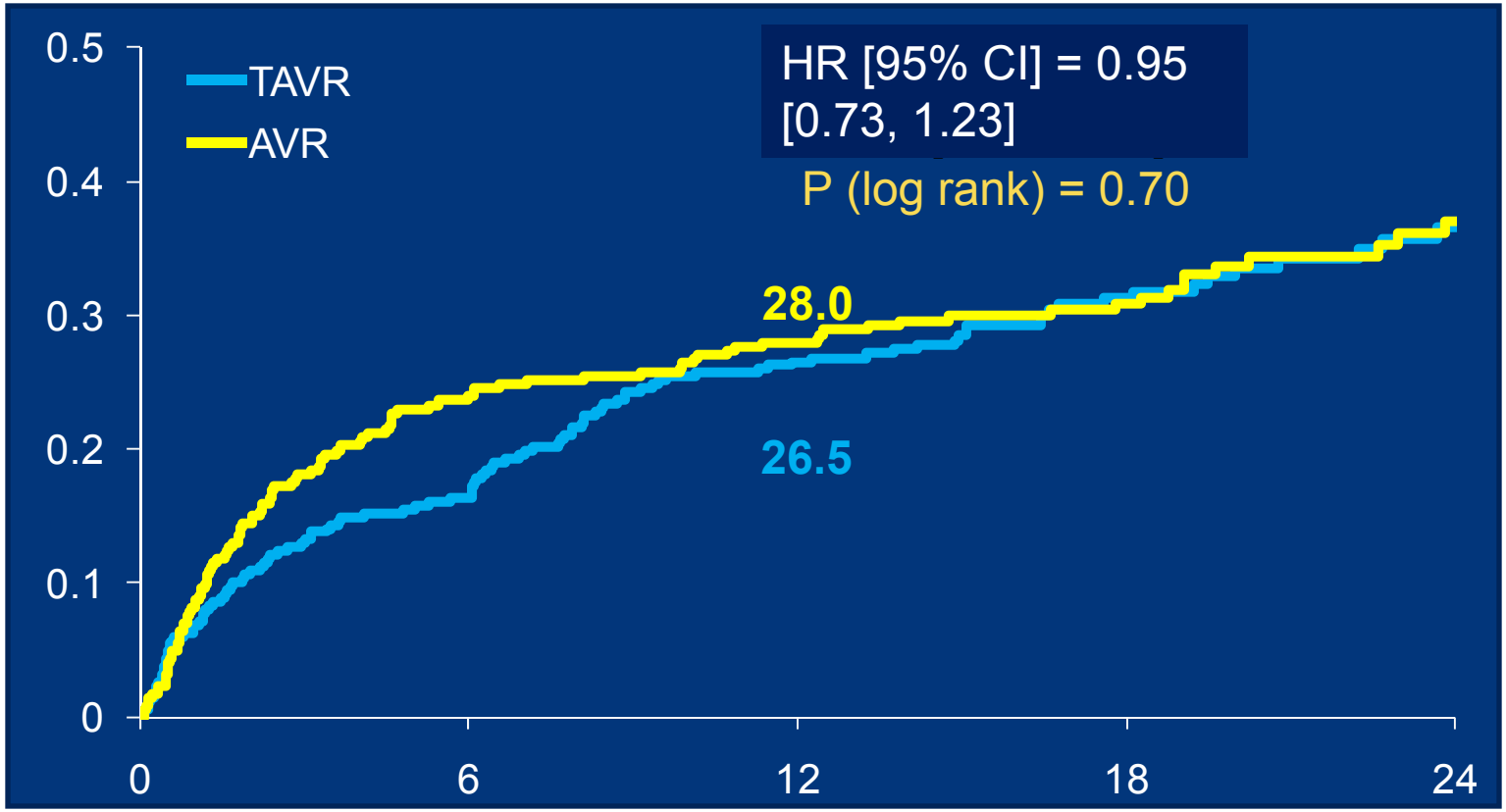
No. at Risk					
Transcatheter	104	83	72	28	8
Surgical	103	72	68	30	9

D Death from Any Cause or Major Stroke



No. at Risk					
Transcatheter	348	289	252	143	65
Surgical	351	247	232	138	63

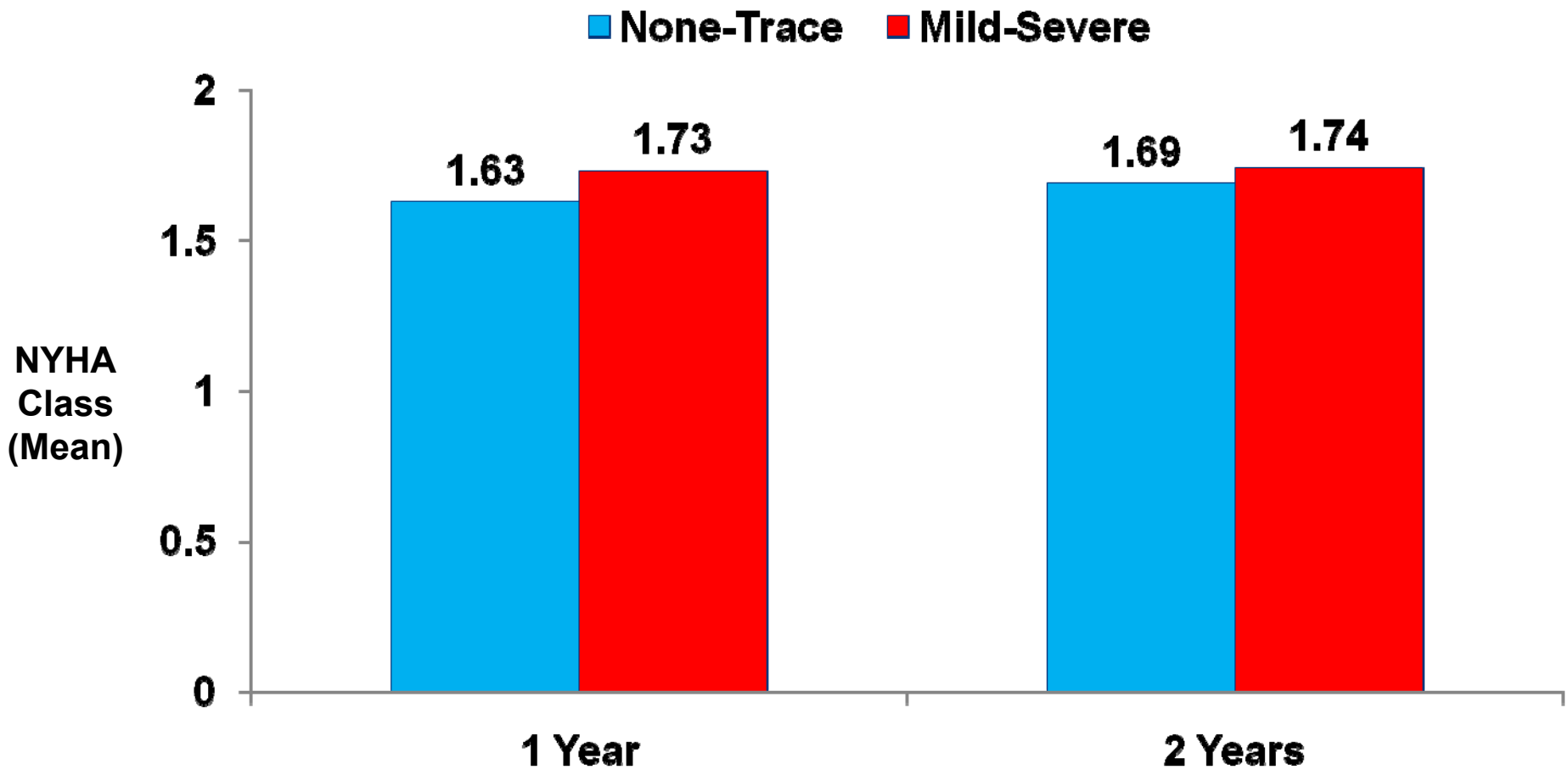
All-Cause Mortality or Major Stroke
All Patients (N=699)



No. at Risk			Months		
TAVR	348	289	252	143	65
AVR	351	247	232	138	63

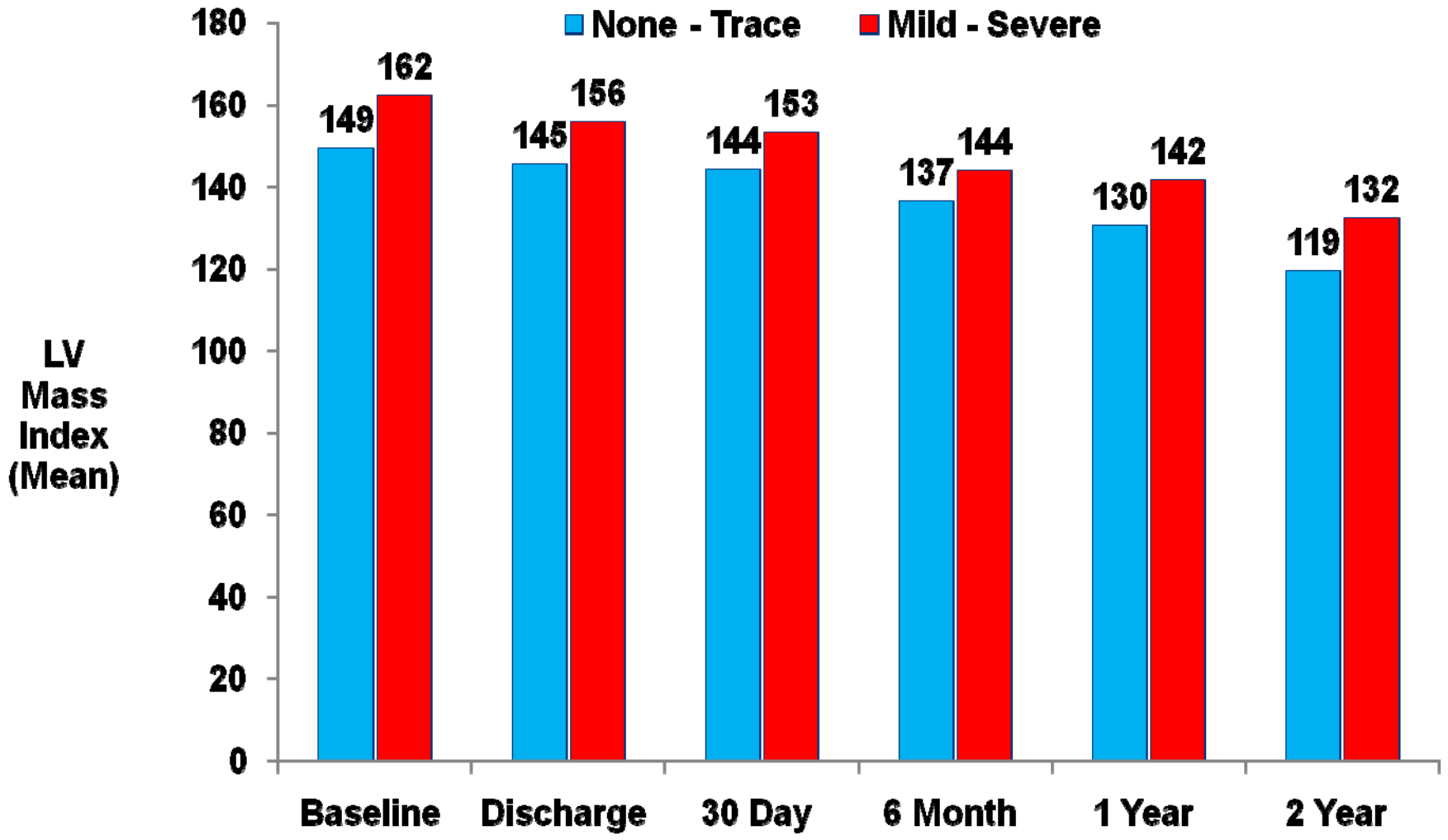
PVL vs NYHA Class

(AT Population)



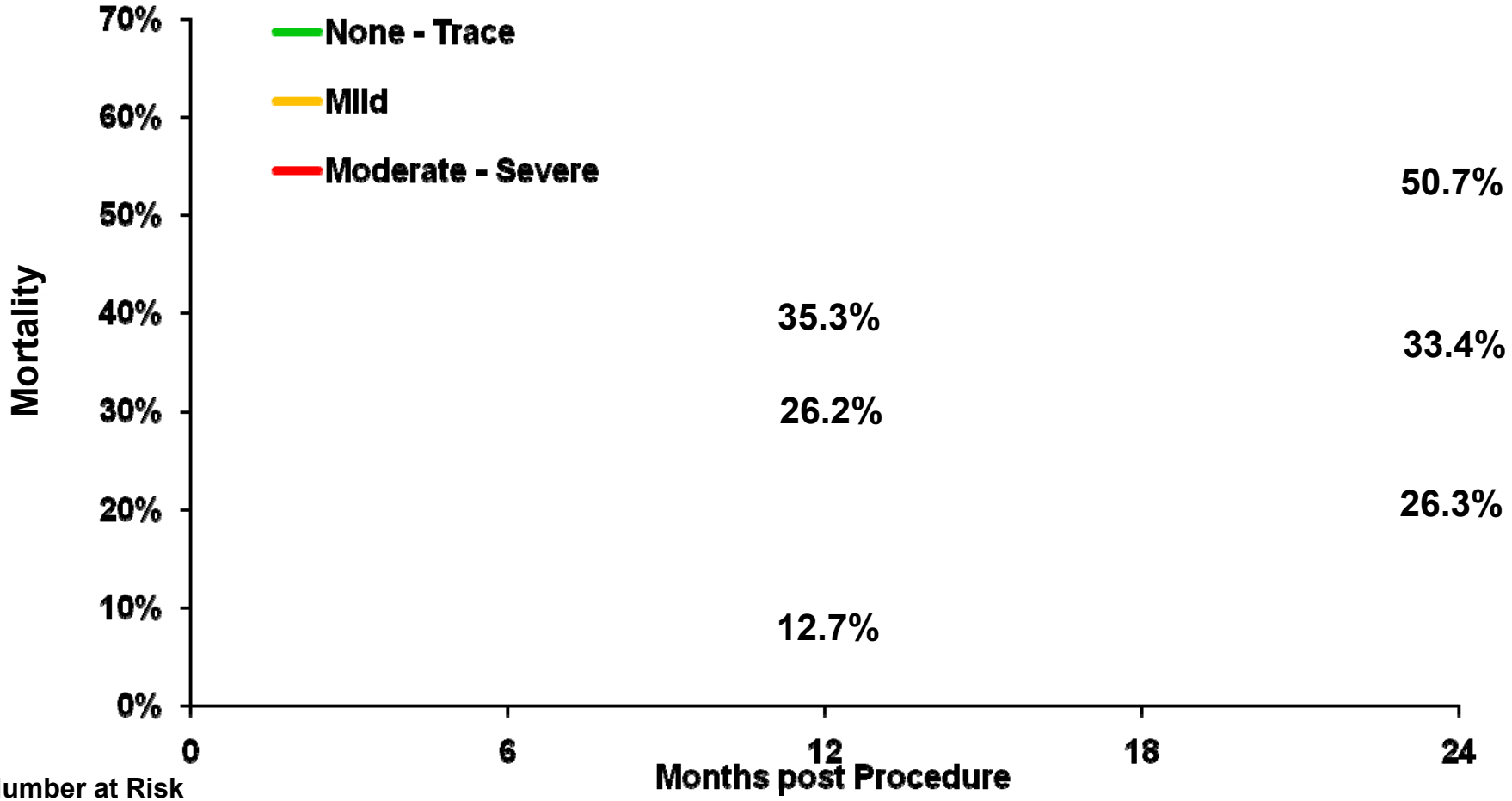
LV Mass Index Stratified by PV Leak

(AT Population)



Impact of Total AR on Mortality TAVR Patients

(AT Population)



Number at Risk					
Non-Trace	135	125	115	101	68
Mild	165	139	121	111	71
Mod-Sev	34	25	22	19	15

CTA Imaging and PVL

Cross-Sectional Computed Tomographic Assessment Improves Accuracy of Aortic Annular Sizing for Transcatheter Aortic Valve Replacement and Reduces the Incidence of Paravalvular Aortic Regurgitation

Hasan Jilaihawi, BSc (Hons), MBChB,* Mohammad Kashif, MD,* Gregory Fontana, MD,† Azusa Furugen, MD, PhD,* Takahiro Shiota, MD,* Gerald Friede, BS, MS,* Rakhee Makhija, MD,* Niraj Doctor, MBBS,* Martin B. Leon, MD,‡ Raj R. Makkar, MD*

Los Angeles, California; and New York, New York

METHODS:

- Comparison of cross-sectional 3D-MSCT vs. 2D-TEE to measure aortic annular for THV sizing

RESULTS:

- 3D-MSCT highest discriminatory value for predicting PVL
- Prospective 3D-MSCT (cw 2D-TEE) valve sizing reduced post-TAVR mod-severe PVL (7.5% vs. 21.9%, p=0.045)

Jilaihawi et al. J Am Coll Cardiol 2012; 59: on-line

Subclassification of Major Bleeding at 1 Year: TAVR vs. AVR (ITT)

Major Bleeding (Hemorrhage per CEC) within 1 year (ITT)		
Criteria of Major Bleeding	**TAVR**	**AVR**
Bleeding causing Death	2 (2 patients)	4 (4 patients)
Bleeding requiring hospitalization or prolonged hospitalization	24 (21 patients)	16 (15 patients)
Bleeding requiring open or endovascular procedure	18 (17 patients)	30 (28 patients)
Bleeding requiring transfusions of more than 3 Units	27 (26 patients)	69 (66 patients)
Total number of Major Bleeding	58*	97*

* Some of the events met more than one criteria of major bleeding, so total do not adds up

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Baseline characteristics: Pooled RCT TAVR vs. CAP (1 of 2)

(ITT Population)

Characteristic	RCT (TAVR) (N=348)	CAP (N=1588)	P-Value
Age - years	84.5 ± 6.4	85.4 ± 6.3	< 0.001
Male	57.8%	51.5%	0.03
STS score	11.7 ± 3.5	11.8 ± 3.9	0.96
NYHA class III/IV	94.3%	95.3%	0.41
Coronary artery disease	74.7%	79.6%	0.05
Previous MI	26.5%	26.5%	1.0
Prior CABG	42.5%	44.2%	0.59
Prior PCI	33.5%	43.8%	< 0.001
Prior BAV	13.2%	26.3%	< 0.001
Peripheral vascular disease	43.2%	45.9%	0.37
Cerebrovascular disease	29.4%	26.9%	0.38

Baseline characteristics: Pooled RCT TAVR vs. CAP (2 of 2) *(ITT Population)*

Characteristic	RCT (TAVR) (N=348)	CAP (N=1588)	P-Value
COPD			
Any	43.7%	43.3%	0.91
Oxygen dependent	17.3%	19.6%	0.45
Creatinine > 2mg/dL	10.8%	9.3%	0.42
Atrial fibrillation	40.7%	43.2%	0.64
Permanent pacemaker	19.8%	22.8%	0.25
Pulmonary hypertension	42.7%	36.8%	0.06
Frailty	15.6%	10.2%	0.008
Echocardiographic Findings			
Aortic valve area - cm2	0.6 ± 0.2	0.7 ± 0.2	0.86
Mean aortic valve gradient - mm Hg	43.5 ± 14.3	44.6 ± 15.0	0.05
Mean LVEF - %	53.1 ± 12.8	52.9 ± 13.1	0.66
Moderate or severe MR	19.6%	22.7%	0.29

Definitions of Low, Medium, and High Enrollment

All RCT Patients

- Low: 1-15 pts
- Medium: 16-34 pts
- High: 35+ pts

Transfemoral RCT Patients

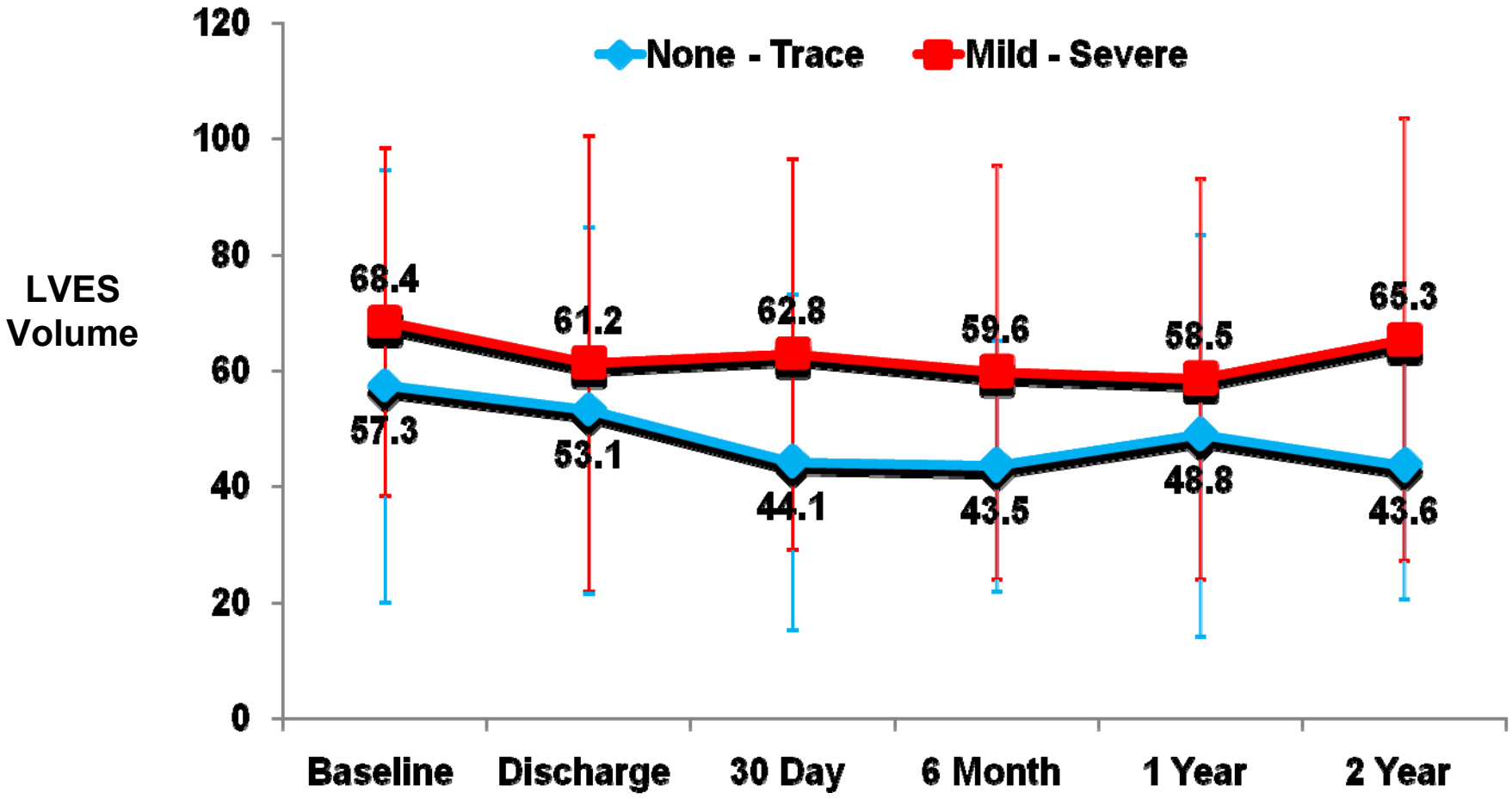
- Low: 1-9 pts
- Medium: 10-24 pts
- High: 25+ pts

Transapical RCT Patients

- Low: 1-9 pts
- Medium: 10-19 pts
- High: 20+ pts

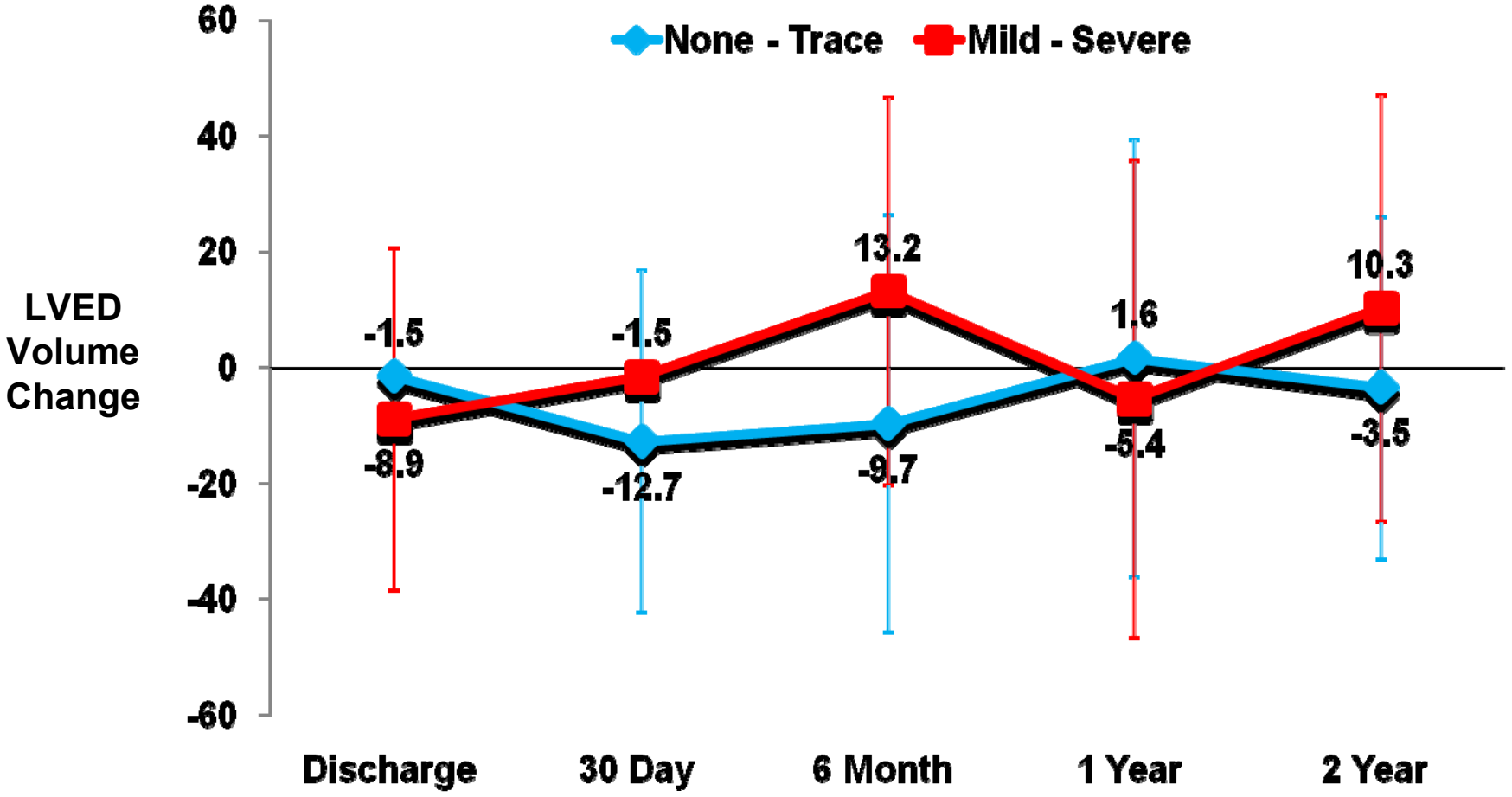
LV Systolic Volume in TAVR PV Leak: None-Trace vs Mild-Severe

(AT Population)

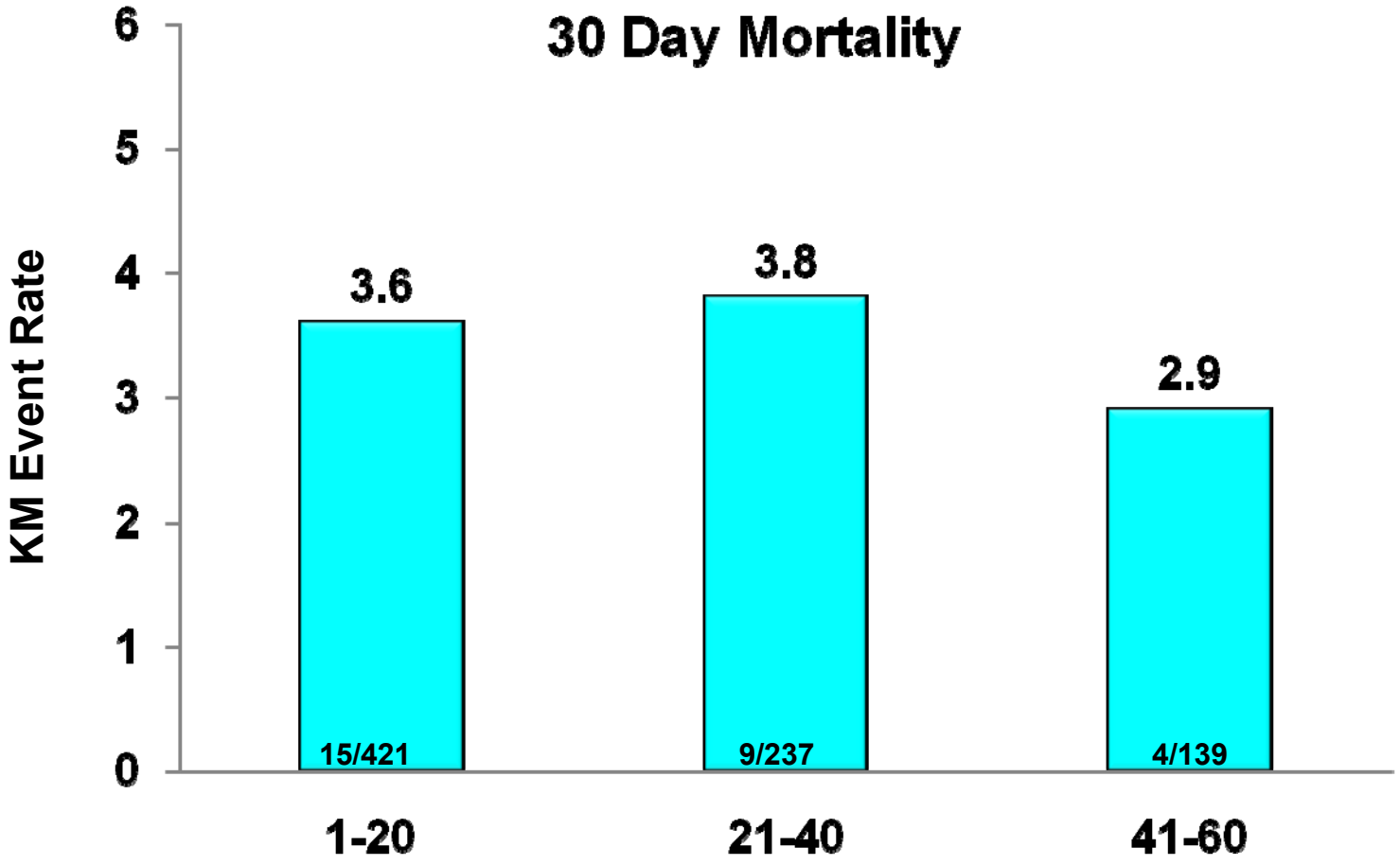


LV Volume Reduction Stratified by PV Leak

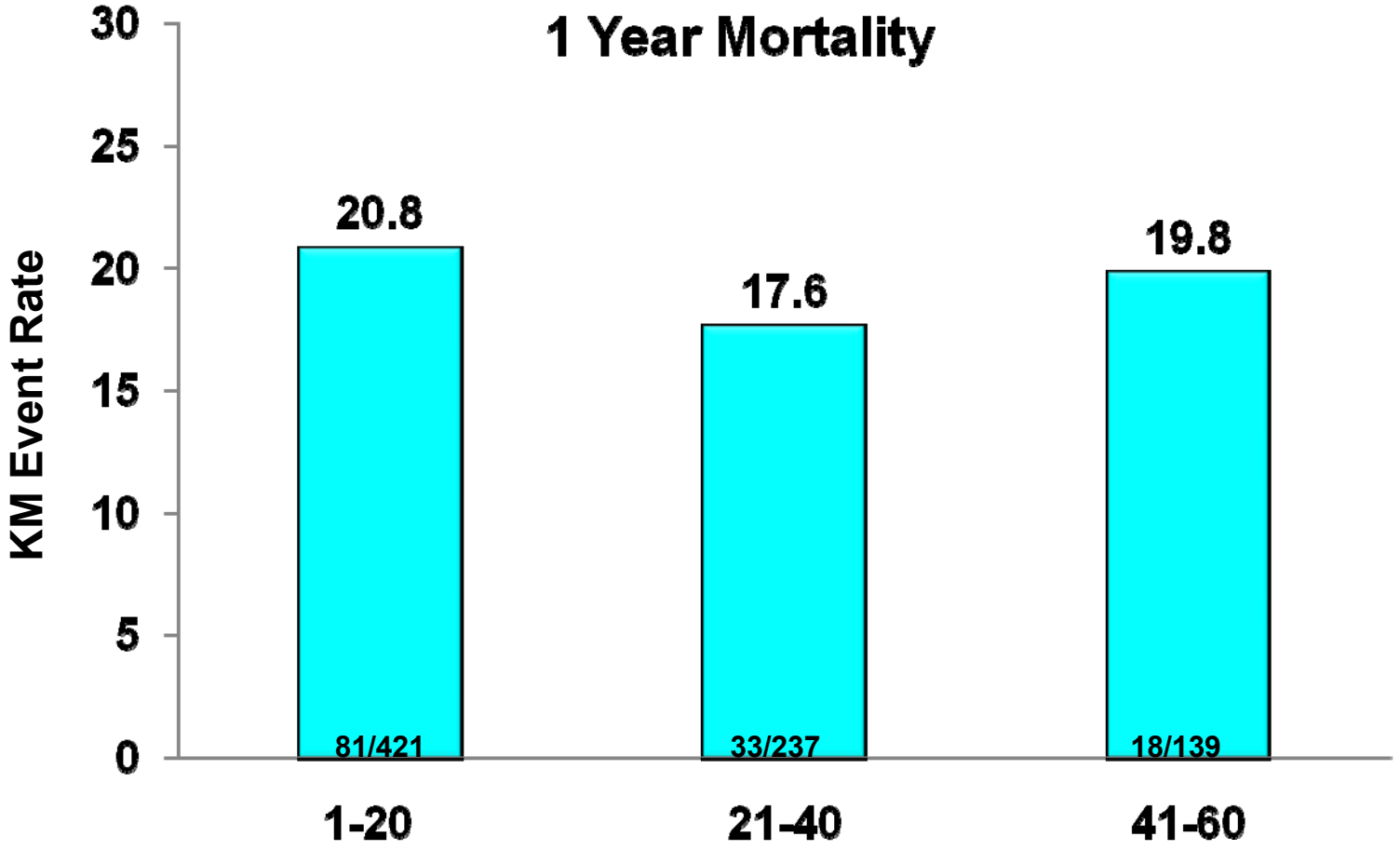
(AT Population)



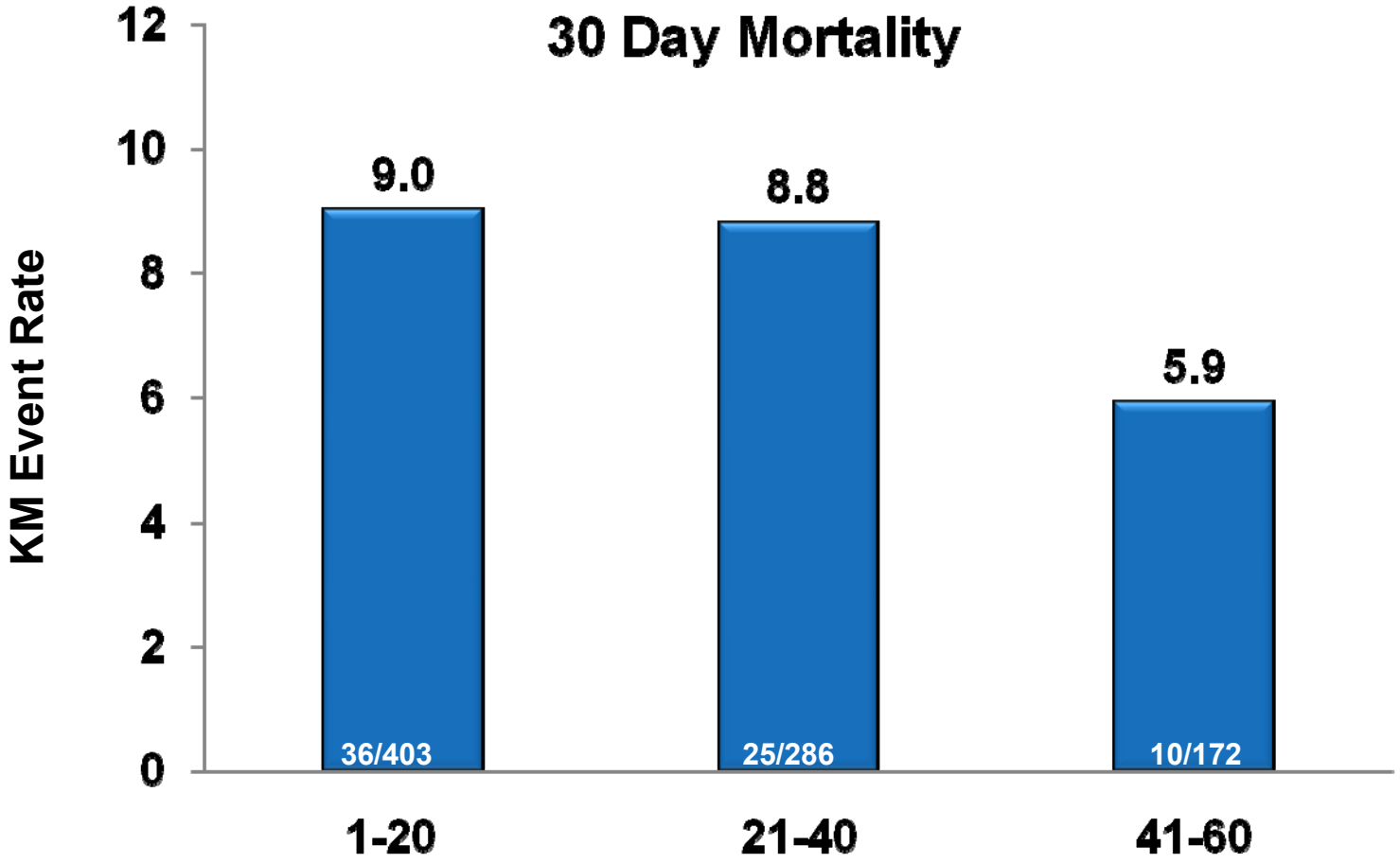
30 Day Mortality by Order of Implant (AT)
All Transfemoral TAVR Patients – RCT & CAP



1 Yr Mortality by Order of Implant (AT)
All Transfemoral TAVR Patients – RCT & CAP



30 Day Mortality by Order of Implant (AT)
All Transapical TAVR Patients – RCT & CAP



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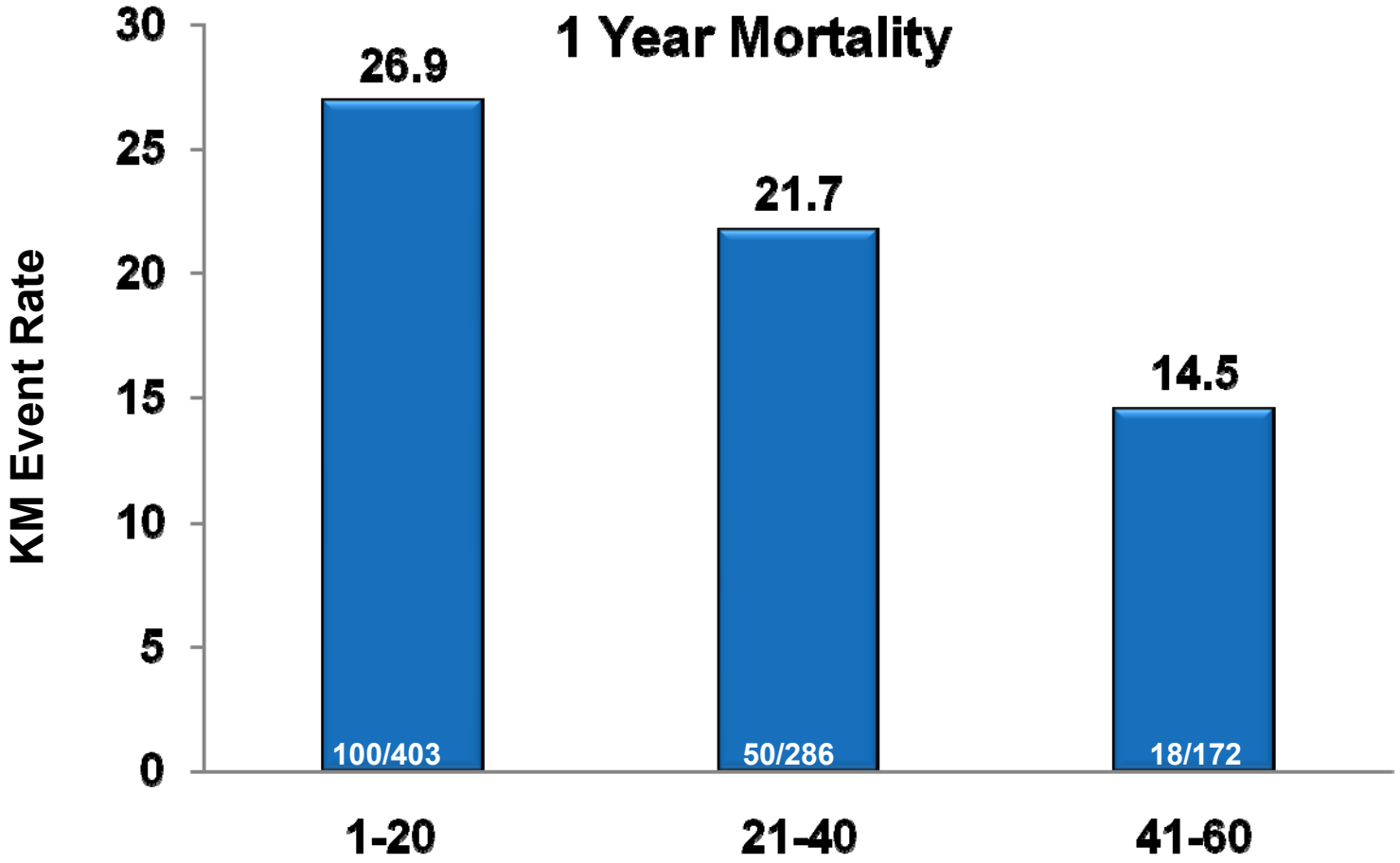

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(ITT Population)

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Age - years	84.5 ± 6.4	85.4 ± 6.3	< 0.001
Male	57.8%	51.5%	0.03
STS score	11.7 ± 3.5	11.8 ± 3.9	0.96
NYHA class III/IV	94.3%	95.3%	0.41
Coronary artery disease	74.7%	79.6%	0.05
Previous MI	26.5%	26.5%	1.0
Prior CABG	42.5%	44.2%	0.59
Prior PCI	33.5%	43.8%	< 0.001
Prior BAV	13.2%	26.3%	< 0.001
Peripheral vascular disease	43.2%	45.9%	0.37
Cerebrovascular disease	29.4%	26.9%	0.38

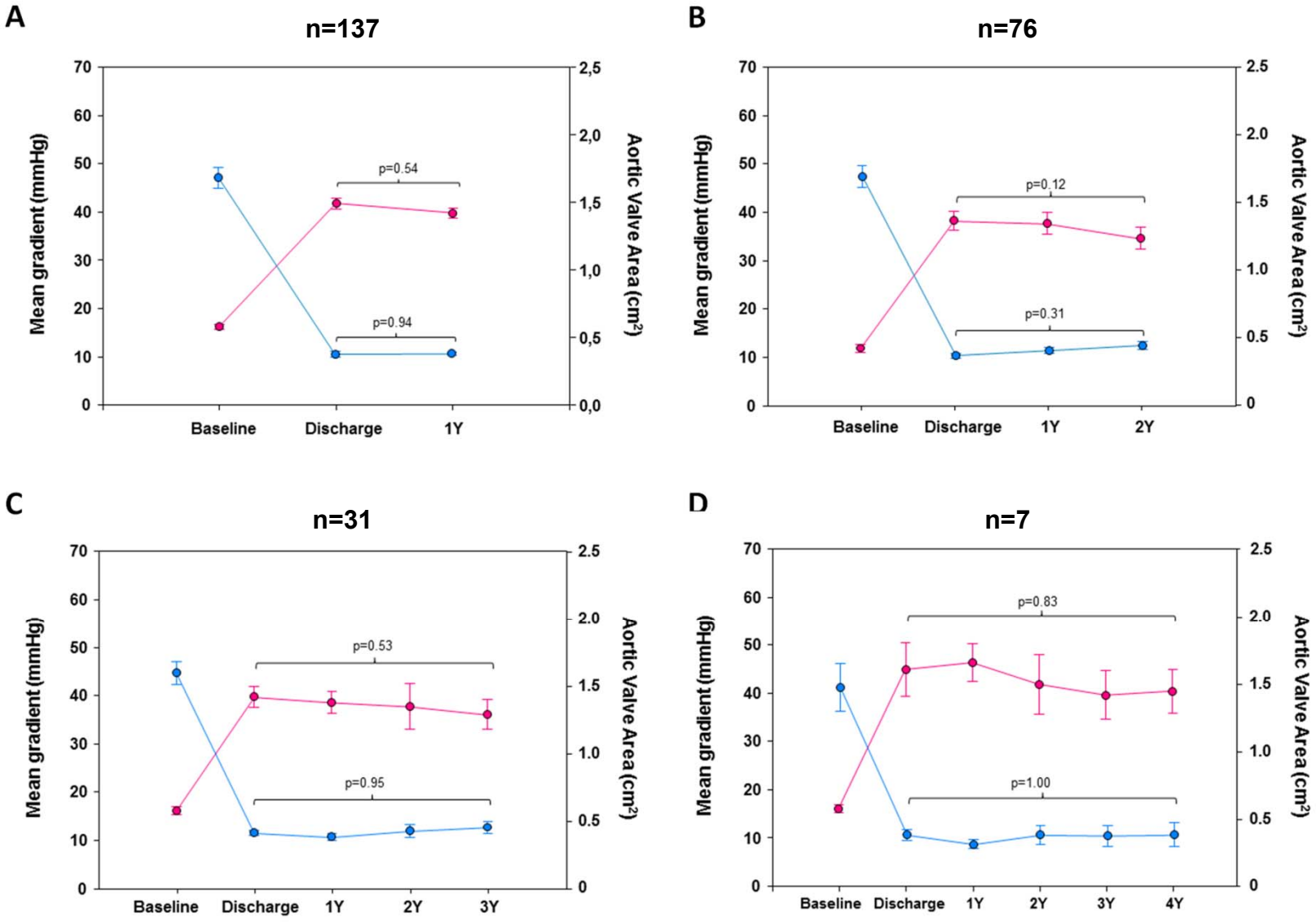
Baseline Characteristics: PV Leak None/Trace Cohorts – TAVR vs AVR (2 of 2)

Characteristic	TAVR (N=158)	AVR (N=271)	p-value
COPD - no./total no. (%)			
Any	65/158 (41.1%)	120/271 (44.3%)	0.55
Oxygen dependent	13/94 (13.8%)	28/173 (16.2%)	0.72
Creatinine > 2mg/dL - no./total no. (%)	11/157 (7.0%)	16/271 (5.9%)	0.68
Atrial fibrillation - no./total no. (%)	33/79 (41.8%)	58/135 (43.0%)	0.89
Permanent pacemaker - no./total no. (%)	30/158 (19.0%)	63/271 (23.2%)	0.33
Pulmonary hypertension - no./total no. (%)	49/132 (37.1%)	81/235 (34.5%)	0.65
Frailty - no./total no. (%)	20/131 (15.3%)	42/234 (17.9%)	0.56
Extensively calcified aorta - no./total no. (%)	1/158 (0.6%)	1/271 (0.4%)	>0.999
Liver disease - no./total no. (%)	2/158 (1.3%)	6/271 (2.2%)	0.72
Echocardiographic Characteristics			
Aortic valve area - cm2	0.7 ± 0.2	0.6 ± 0.2	0.18
Mean aortic valve gradient - mm Hg	42.4 ± 13.2	43.4 ± 14.2	0.46
Mean LVEF - %	54.4 ± 12.8	53.7 ± 12.4	0.60
Moderate or severe MR - no./total no. (%)	29/152 (19.1%)	53/259 (20.5%)	0.80

Neurological Events at 30 Days and 1 Year All Patients (N=699)

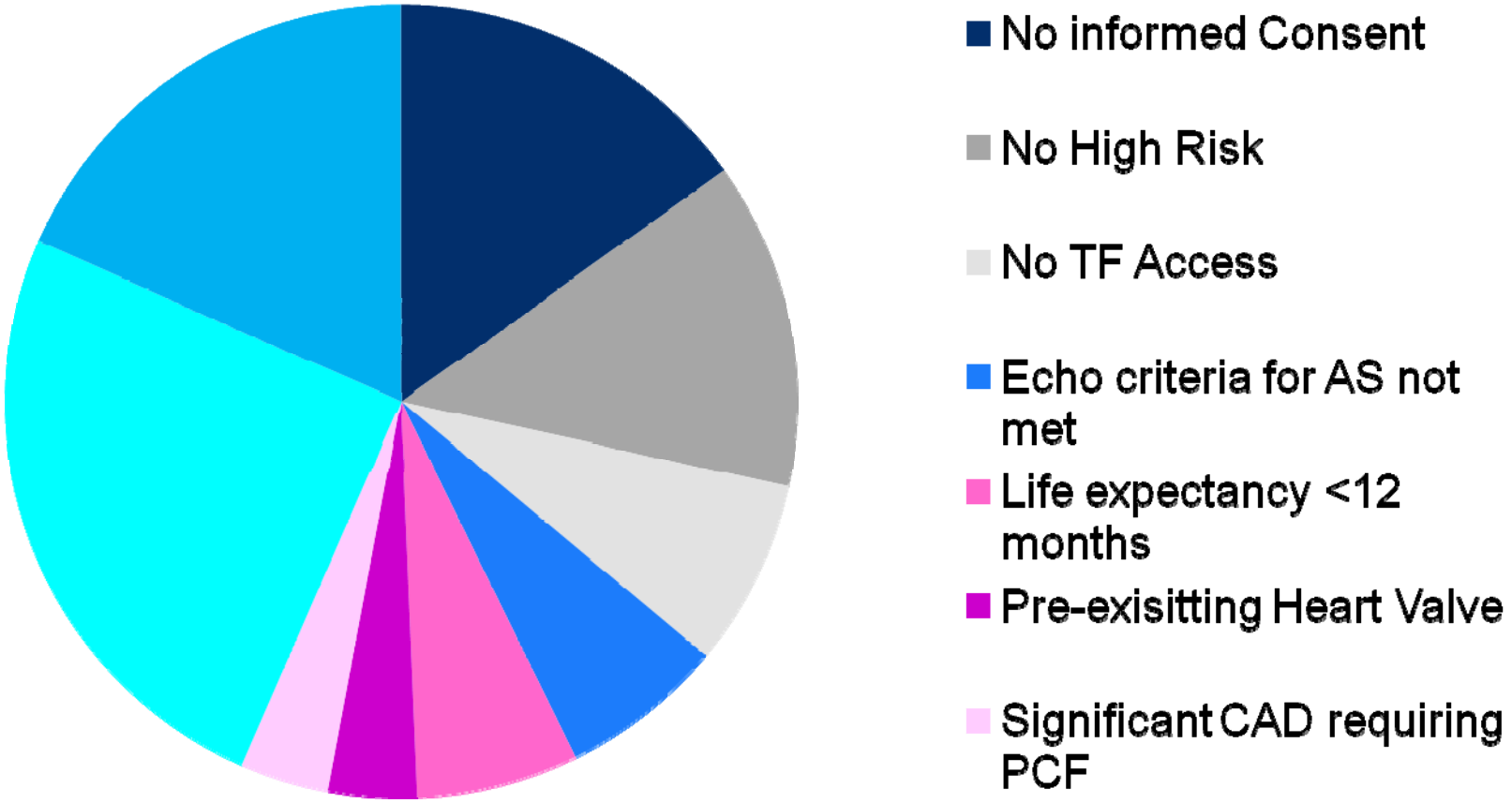
	30 Days			1 Year		
Outcome	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*
All Stroke or TIA – no. (%)	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
TIA – no. (%)	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
All Stroke – no. (%)	16 (4.6)	8 (2.4)	0.12	20 (6.0)	10 (3.2)	0.08
Major Stroke – no. (%)	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07
Minor Stroke – no. (%)	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Death/maj stroke – no. (%)	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68

Canadian Long-term Data
Mean Gradient and Aortic Valve Area Over Time (Edwards SAPIEN valve)



Main Reasons for Screen Failure (n > 100)

Total Screen Failures: 2939



All Concomitant Procedures in AVR

Category	ALL	CABG	VALVE	AORTA	Other
Preop / planned	20	13	3	2	2
Intraop / unplanned	22	6	1	8	7
Unplanned / borderline	5	0	4	1	0

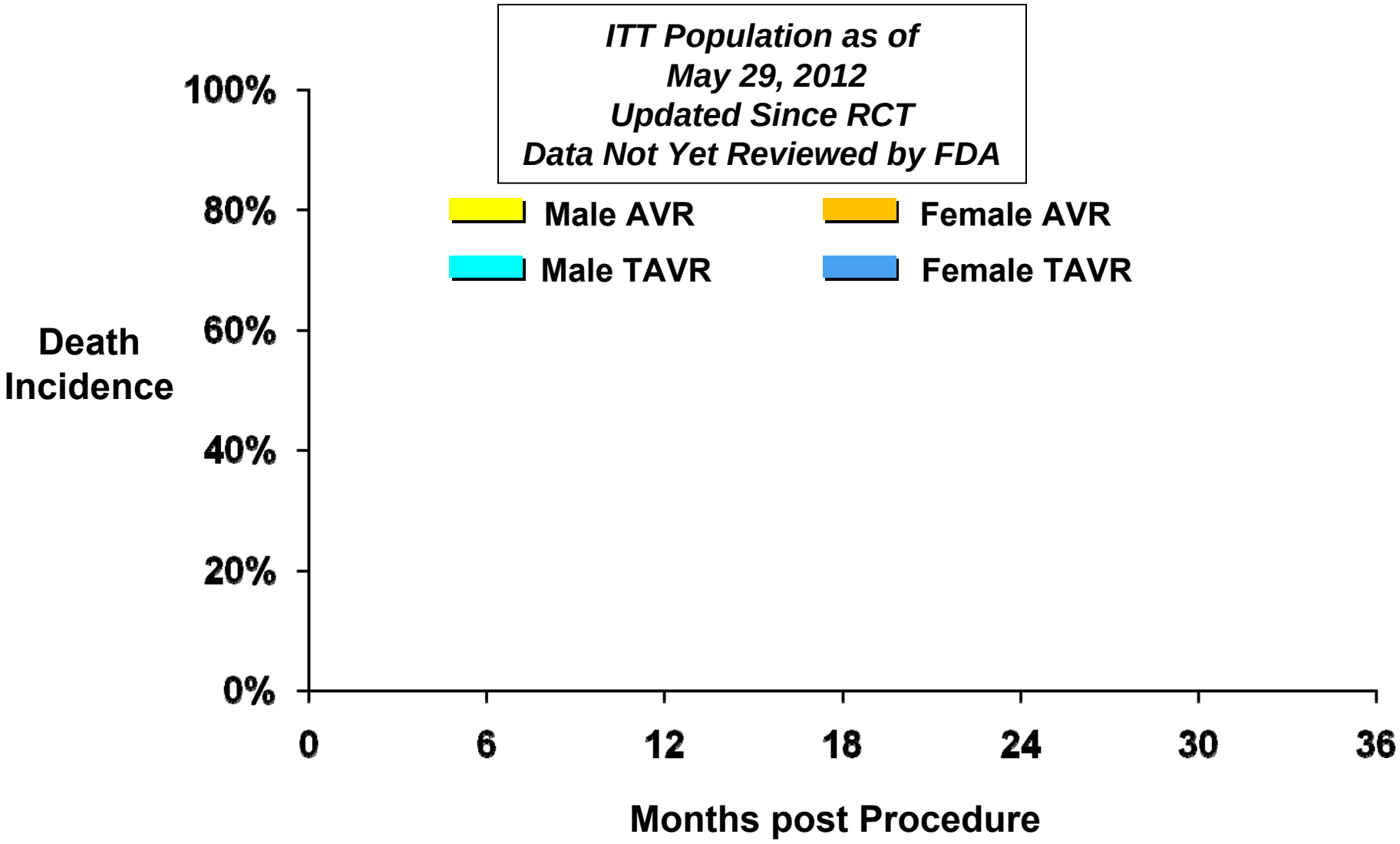
- 30 day mortality 1/20 5%
- 1 year mortality 6/20 30%

- 50 concomitant cases reported
- 3 excluded after review
- All cases reviewed by two surgeons - one of the two surgeons was commissioned to perform an independent review

Surgical AVR Outcomes – OE Ratio

- Using an established predictive risk model (STS), the expected (“E”) 30-day mortality after AVR was 11.8%.
- The observed (“O”) 30-day mortality in the as-treated AVR control group was 8.0%.
- O:E = 0.68 indicates better than predicted surgical outcomes in the control AVR patients.
- There were no significant site or surgeon differences.

Death by Gender



Clarification of Gender %

Raw Percentages

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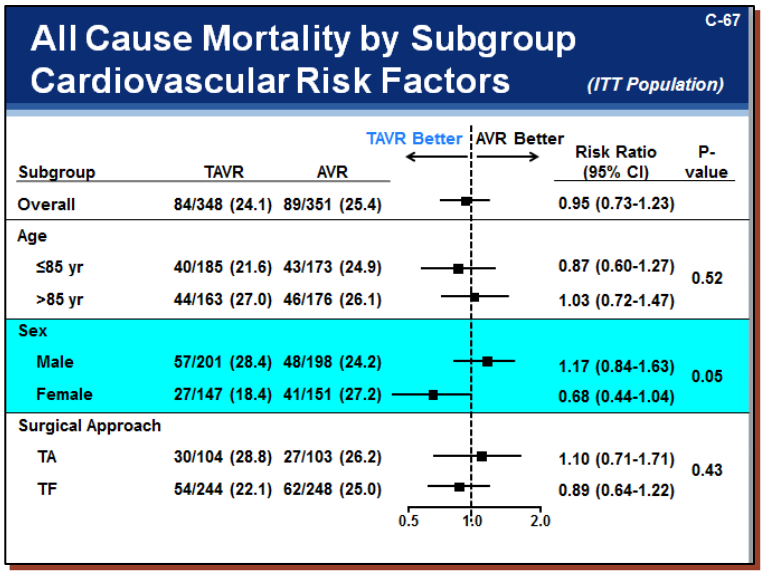
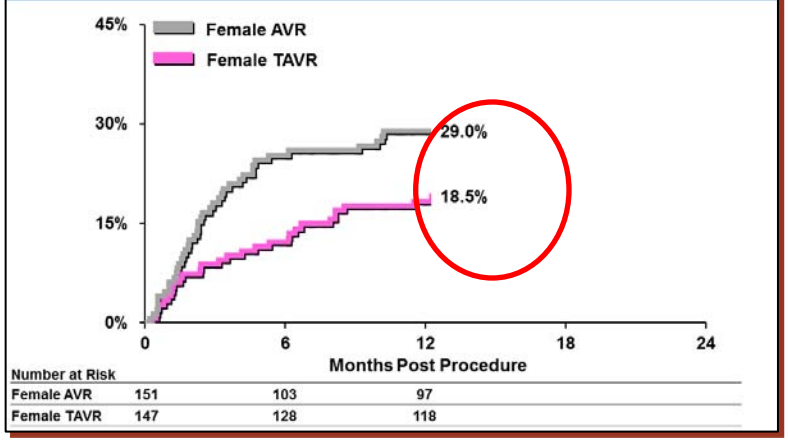
All Cause Mortality by Subgroup Cardiovascular Risk Factors *(ITT Population)*



Subgroup	TAVR	AVR	Risk Ratio (95% CI)	P-value
Overall	84/348 (24.1)	89/351 (25.4)	0.95 (0.73-1.23)	
Age				
≤85 yr	40/185 (21.6)	43/173 (24.9)	0.87 (0.60-1.27)	0.52
>85 yr	44/163 (27.0)	46/176 (26.1)	1.03 (0.72-1.47)	
Sex				
Male	57/201 (28.4)	48/198 (24.2)	1.17 (0.84-1.63)	0.05
Female	27/147 (18.4)	41/151 (27.2)	0.68 (0.44-1.04)	
Surgical Approach				
TA	30/104 (28.8)	27/103 (26.2)	1.10 (0.71-1.71)	0.43
TF	54/244 (22.1)	62/248 (25.0)	0.89 (0.64-1.22)	

KM Percentages

All-cause Mortality – Female *(ITT Population)*



Number at Risk			
Female AVR	151	103	97
Female TAVR	147	128	118

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12 Month Mortality Analysis by Gender

Cohort Studied	Males		Females	
	ITT	AT	ITT	AT
TAVR RCT	28.5%	27.4%	18.5%	18.6%
AVR RCT	25.2%	22.7%	29.0%	28.6%
TAVR CAP	25.9%	25.4%	18.5%	17.5%

Note:
RCT = Randomized Controlled Trial
CAP = Continued Access Protocol

Median Survival

ITT Population as of
May 29, 2012
Updated Since RCT
Data Not Yet Reviewed by FDA

ITT RCT	Median	Mean
AVR	1136 days	826
TAVR	1209	956
Delta	73	130

PMA submission data could not be used because the TAVR arm had not yet reached 50% death rate, hence median could not be computed.

Note: Mean survival time is underestimated because the largest observation was censored.

Perspectives for Selecting AVR vs TAVR in High Risk Surgical Patients